



6. The method of claim 1, 2, 3, or 4 wherein the preparation releases the form of Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.
7. The method of claim 1, 2, 3, or 4 wherein the preparation is in capsule form.
8. The method of claim 1, 2, 3, or 4 wherein the preparation is in tablet form.
9. The method of claim 1, 2, 3, or 4 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.
10. The method of claim 1, 2, 3, or 4 wherein the preparation comprises a plurality of microgranules each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically

acceptable salt thereof associated with a wetting agent and wherein the form of Diltiazem is mixed with the wetting agent.

11. The method of claim 1, 2, 3, or 4 wherein the preparation comprises a plurality of microgranules each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the form of Diltiazem is mixed with the wetting agent wherein the wetting agent assists to maintain the solubility of the form of Diltiazem in each bead, ensuring that the solubility of the form of Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

12. The method of claim 1, 2, 3, or 4 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the membrane comprises a water-dispersible or water-soluble polymer and a

water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

13. The method of claim 1, 2, 3, or 4 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the preparation comprises a mixture of the form of Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

14. The method of claim 1, 2, 3, or 4 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the membrane comprises a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

15. The method 1, 2, 3, or 4 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the form of diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

16. The method of claim 9 wherein the form of Diltiazem is mixed with the wetting agent and the membrane comprises N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propenyl)oxy]-chloride enthanaminium polymer with ethyl-2-propenoate and mythyl-2-methyl-2-propenoate, an acrylic polymer and plasticizer combined to form the membrane thereby providing a mechanism

of release from this membrane which "washes" the form of diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

17. The method of claim 1, 2, 3, or 4 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in the release of the form of Diltiazem from the preparation.

18. The method of claim 1, 2, 3, or 4 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in the release of the form of Diltiazem from the preparation and wherein the dissolution agent is an organic acid selected from the group consisting of adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid which permits the form of diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the higher pH regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

54 A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 18 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina over a twenty-four hour period.

55 The method of claim 1, 2, 3, or 4 wherein the preparation contains 180 mg of Diltiazem.

56 The method of claim 1, 2, 3, or 4 wherein the preparation contains 360 mg of Diltiazem.

57 The method of claim 1, 2, 3, or 4 wherein the preparation contains 420 mg of Diltiazem.

58 A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from the about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation, for providing C_{max} of Diltiazem in the blood at between about 10 hours and about 17 hours (T_{max}) after administration of the preparation, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem.

together with adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants.

75. The method of claim 74 wherein the microgranules are in capsule form
76. The method of claim 74 wherein the microgranules are in table form.
77. The method of claim 74, 75, or 76 wherein the core and membrane comprise:
 - (i) in the core,
 - (a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
 - (b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

81. The method of claim 1, 2, 3, or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

82. The method of claim 1, 2, 3, or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

83. The method of claim 1, 2, 3, or 4 in table form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

84. The method of claim 1, 2, 3, or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein such microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

85. The method of claim 1, 2, 3, or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

86. The method of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is

a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

87. The method of claim 1, 2, 3, or 4 in table form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

88. The method of claim 1, 2, 3 or 4 in table form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt

thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

89. The method of 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

90. The method of claim 1, 2, 3, or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core

comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

91. The method of claim 1, 2, 3 or 4 in table form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associate with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

92. The method of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of

active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

93. The method of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a

water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

94. The method of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

95. The method of claim 1, 2, 3 or 4 in table form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with a wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

96. The method of claim 1, 2, 3 or 4 in table for wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane

and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

97. The method of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with the wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse

conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

98. The method of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble

polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

99. The method of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

100. The method of claim 1, 2, 3 or 4 in tablet form wherein the preparation a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

101. The method of claim 1, 2, 3 or 4 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt

thereof associated with the wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

102. The method of claim 1, 2, 3 or 4 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled

preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with the wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

103. The method of claim 1, 2, 3 or 4 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule

comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

104. The method of claim 1, 2, 3 or 4 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of

active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).